Claims Rejections – 35 U.S.C. § 112, First Paragraph

Claims 30-37 stand rejected under 35 U.S.C. § 112, first paragraph, on the grounds that the specification is purportedly lacking in enablement for combinations of C_3-C_{10} polyalkylene glycols and potassium channels blockers other than 4-aminopyridine.

In response to the rejection of claims 30-37 under 35 U.S.C. § 112, first paragraph, claim 30 has been amended to limit the claimed synergistic combination to that of polyethylene glycol and 4-aminopyridine, while claims 31-37 have been cancelled.

Claims Rejections – 35 U.S.C. § 112, Second Paragraph

Claims 22-43 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention.

The Examiner specifically maintains that the recitation "said method resulting in ... after said spinal cord is treated" in claim 22, lines 4-6 and claim 38, lines 2-6, is indefinite as to the method steps required to achieve the recited results.

In response to this rejection of claims 22 and 38, those claims have been amended to clarify the steps required to achieve the recited results. In particular, claims 22 and 38 have been amended to recite that the claimed polyalkyene glycol is applied "in an amount effective to increase a compound action potential in said injured spinal cord relative to a level of said compound action potential immediately after said injury and to increase behavioral recovery after said spinal cord is treated." It is therefore clear that the application of a therapeutically effective amount is the step necessary to achieve the desire results.

With respect to claims 22 and 38, the Examiner also points out that the expression "as soon as possible" renders those claims indefinite as to the time of contact between the injured spinal cord and the polyalkylene compounds encompassed by the claims.

In response to this point, claims 22 and 38 have been amended to delete the phrase "as soon as possible." The time of contact is now clearly specified.

With reference to claim 30, the Examiner contends that the recitation "said method resulting in a synergistic increase ... behavior in said patient" in lines 4-6 renders the claim indefinite as to the method steps required to achieve the recited results.

In response to this rejection of claim 30, that claim has been amended to clarify the steps required to achieve the recited results. In particular, claim 30 has been amended to recite "contacting said injured spinal cord with a potassium channel blocker ... so as to produce a synergistic increase in restoration of nerve function and reflex behavior in said patient." Thus, the recited synergistic increase is produced by the contacting of the injured spinal cord with the potassium channel blocker.

With reference to claims 30 and 40, the Examiner contends that the expression "before, during or after contacting said spinal cord with said polyalkylene glycol" renders the claims indefinite.

In response to this rejection of claims 30 and 40, those claims have been amended to recite that the contacting the spinal cord with the potassium channel blocker is within an effective time of contacting the spinal cord with polyethylene glycol so as to produce a synergistic increase in restoration of nerve function and reflex behavior in the patient. The timing of application of the potassium channel blocker is therefore tied to the effectiveness of the application.

With respect to claims 22 and 38, the Examiner maintains that the phrase "at least partial restoration" is a relative term which renders the claims indefinite. According to the Examiner, the phrase is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

In response to this rejection of claims 22 and 38, those claims have been amended to eliminate the phrase "at least partial restoration" and to refer instead to the increase in compound action potential relative to the level thereof immediately after the injury.

Claims Rejections - 35 U.S.C. §§ 102 and 103

Claims22, 24-29, 38, and 39 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Davis et al. (Journal of Spinal Disorders, 1990; 3(4): 299-306).

Claims 23, 30-37, and 40-43 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Davis et al. (Journal of Spinal Disorders, 1990; 3(4): 299-306) in view

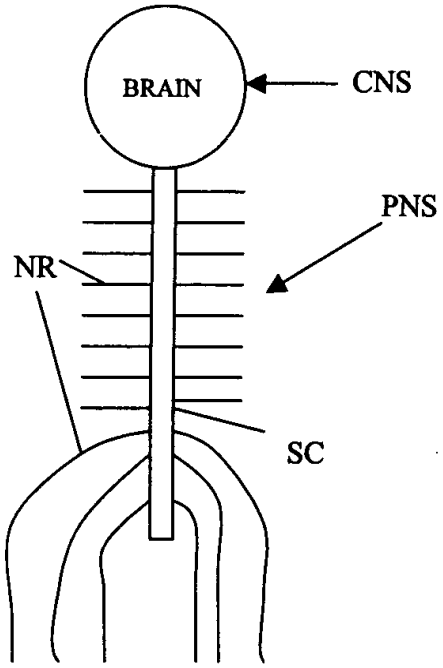
of Brown (Clinical Orthopedics and Related Research, 1977; 129: 72-78) and Potter et al. (Clin. Invest. Med., 19(4), Suppl.: S80, #533).

Applicants respectfully traverse the rejection of claims 22, 24-29, 38, and 39 under 35 U.S.C. § 102(b) as being anticipated by Davis et al. (Journal of Spinal Disorders, 1990; 3(4): 299-306). As pointed out by the Examiner, that reference teaches the deposition of methylpregnisolone containing PEG 3350 on an exposed nerve root during a spinal lumbar surgery for disc excision and retraction of the nerve root with incision. That description of the teachings of Davis et al. is correct. However, the Examiner goes on to characterize this incision as being a form of spinal cord injury. That characterization is incorrect. Davis et al. teach ***nothing*** about the application of PEG to an injured spinal cord for the simple reason that a nerve root is located ***outside of the spinal column*** and is part of the ***peripheral nervous system***.

The nerve fibers of the peripheral nervous system are ***vastly different*** from the nerve fibers of the central nervous system, particularly including the spinal cord. The anatomy of nerves of the peripheral nervous system is different from the anatomy of nerves in the central nervous system (brain and spinal cord). Severing of or injury to the nerve roots ***never*** results in paralysis, whereas injury to the spinal cord frequently does result in paralysis. Moreover, the nerves of the peripheral nervous system are capable of ***regeneration*** whereas the nerves of the central nervous system, particularly the spinal cord are ***not*** capable of regeneration. Accordingly, it is not surprising that nerve roots, which are fibers located outside of the spinal cord and which are not part of the spinal cord, might experience some restoration after an injury and upon proper treatment. However, that a treatment of an injured nerve root might have a positive effect on the nerve root is ***no indication*** whatsoever that the same treatment will have any effect whatsoever on a spinal cord injury. As stated in the Declaration of applicant Dr. Richard B. Borgens submitted in response to the previous Office Action, any restoration of nerve

function to an injured spinal cord *in vivo* is a surprising and unexpected result. That the application, to an injured nerve root, of a composition incidently containing PEG has a therapeutic effect on the nerve root provides no expectation whatsoever that the purposeful application of PEG to an injured spinal cord would have any therapeutic effect on the spinal cord.

To clarify the differences between the nerve roots and the spinal cord, applicants provide the following drawing.



Further to the discussion above, the brain and the spinal cord SC form the central nervous system CVS, while the nerve roots NR are part of the peripheral nervous system PNS and are located outside of the spinal cord SC. (The peripheral nervous system PNS additionally includes other nerves in the body.) The spinal cord SC is located completely inside of the vertebral column (not separately shown). Fibers of the spinal cord SC may be processes of nerve cells whose cell bodies are located along, but outside of, the spinal cord SC. Those cells have nerve processes which together with nerve processes leaving

the spinal cord SC are the nerve roots NR. These extend from the spinal cord SC to peripheral areas of the body at each vertebral level.

This characterization of the spinal cord and nerve roots may be easily verified by consulting any reference work on anatomy. Attached hereto, for example, as APPENDIX B is a print-out of a page from the World Wide Web, at the Web address www.spine-health.com/topics/anat/a04.html. The description on that Web page indicates that the nerve roots are different from the spinal cord and extend outwardly from the spine: "The spinal cord does not run through the lumbar spine. After the spinal cord stops in the lower thorasic spine, the nerve roots come off the bottom of the cord like a 'horse's tail.'" Also: the "nerve roots run through the bony canal, and at each level a pair of nerve roots exists the spine."

Also attached hereto as APPENDIX C is a copy of an excerpt from "Wheeless' Textbook of Orthopaedics," also taken from the World Wide Web at site www.medmedia.com/o11/44.htm. The description of spinal nerves indicates that the nerves leave the spinal column or vertebral canal through intervertebral foramina.

It is to be noted, with respect to the teachings and implications of Davis et al., that one of ordinary skill in the art would not, on the basis of that reference, apply a polyalkylene to a spinal cord injury for a therapeutic purpose. The purpose of PEG in the methylpregnisolone composition is to increase solubility . PEG is used ubiquitously in medical and cosmetic applications for this purpose: to bond to an insoluble chemical composition in order to render that composition soluble in aqueous solutions.

As pointed out in a prior Amendment, the present invention has evidenced unexpected activity in restoring nerve function and behavioral recovery in mammalian patients. The present invention could not possibly be predicted from the prior art and represents an unexpected result over the disclosure of the prior art. In the present invention, as described in the examples of the specification, a dramatic response to treatment with PEG was realized in experimental animals (guinea pigs). In the present invention 100% of experimental animals treated with PEG evidenced substantial return of cord nerve impulse conduction vs. 0% of controls and 90% PEG-treated guineas pigs exhibited a return of behavior vs. 17% of controls. These results represent an unexpected

result and evidence that the present method exhibits great potential to treat patients who have suffered spinal cord injury.

As noted above, the teachings of Davis et al. could not possibly provide any level of expectation which might approximate the *in vivo* treatment of an injured spinal cord. The differences between the spinal cord (CNS) and nerve roots (PNS) are too substantial to imply or suggest treatment of an injured spinal cord as compared to the treatment of exposed nerve roots.

Turning now to the Examiner's rejection of the claims which utilize a potassium channel blocker in combination with an polyalkylene glycol to synergistically treat spinal cord injury, applicants respectfully submit that the disclosures of Potter et al. and/or Brown and the disclosure of Davis et al. fail to render those claims obvious. As discussed hereinabove, the present invention makes use of polyalkylene glycol compounds to treat spinal cord injury in mammalian patients. As discussed, the teachings and implications of Davis et al. in no way renders the present invention anticipated or obvious. The disclosures of Potter et al. and Brown are essentially inapposite to the present invention inasmuch as these references do not in any way cure the deficiencies of the prior art. Potter teaches the use of 4-aminpyridine in spinal cord injuries but fails to even mention polyalkylene glycol. Neither Potter et al. nor Brown recognizes the unexpected properties the polyalkylene glycols exhibit in treating spinal cord injury. Neither of these references even mentions polyalkylene glycols as a possible treatment for spinal cord injury. Because of the deficient disclosures of Potter et al. and Brown, it is respectfully submitted that the claimed invention is patentable over these references.

It is to be noted that the amendments made herein could not have been made earlier owing to the fact that the rejections addressed herein were made only in the final Office Action. The amendments made herein are deemed to reduce the issues for appeal: all of the § 112 issues are believed to be overcome by the amendments made herein.

For the above reasons, applicants respectfully assert that the claims set forth in the amendment to the application of the present invention are now in compliance with 35

U.S.C. Applicants respectfully submit that the present application is now in condition for allowance and such action is earnestly solicited.

Respectfully submitted,

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Dated: February 22, 2002

By: _____

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CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as First Class Mail in an envelope addressed to: "Commissioner for Patents, Washington, D.C. 20231" on February 22, 2002.

_____

R. Neil Sudol, Reg. 31,669

APPENDIX A

Amend claim 22 as follows:

22. (Once Amended) A method of treating a mammalian patient having suffered an injury to its spinal cord, said method comprising contacting [said] the injured spinal cord [as soon as is possible and] within a period no greater than about 24 hours after said injury with [an effective amount of] a C_1-C_{10} polyalkylene glycol[, said method resulting in at least partial restoration of nerve function] in an amount effective to increase a compound action potential in said injured spinal cord relative to a level of said compound action potential immediately after said injury and [an increased] to increase behavioral recovery after said spinal cord is treated.

Amend claim 30 as follows:

30. (Once Amended) The method according to claim 22, wherein said polyalkylene glycol is polyethylene glycol and wherein said method further comprises the step of contacting said injured spinal cord with [an effective amount of] a potassium channel blocker [before, during or after] in the form of 4-aminopyridine in an effective amount and within an effective time of contacting said spinal cord with said [polyalkylene] polyethylene glycol[, said method resulting in] so as to produce a synergistic increase in restoration of nerve function and reflex behavior in said patient.

Amend claim 38 as follows:

38. (Once Amended) A method of treating a mammalian patient having suffered an injury to its spinal cord, said method comprising contacting [said] the injured spinal cord [as soon as is possible and] within a period no greater than about 24 hours after said injury with [an effective amount of] polyethylene glycol[, said method resulting in at least partial restoration of nerve function] in an amount effective to increase a compound action potential in said injured spinal cord relative to a level of said compound action potential immediately

after said injury and [an increased] to increase behavioral recovery after said spinal cord is treated.

Amend claim 40 as follows:

40. (Once Amended) The method according to claim 38 further comprising the step of [contact] contacting said injured spinal cord with [an effective amount of] a potassium channel blocker [before, during or after] in the form of 4-aminopyridine in an effective amount and within an effective time of contacting said spinal cord with said polyethylene glycol.

APPENDIX B